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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,820	07/21/2000	Alan D. Attie	960296.97290	4397

7590 12/17/2003

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/620,820	ATTIE ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/21/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-12 and 17 are pending in the application.

This Office Action is in response to the Amendment filed on 9/2/03.

Response to Amendment

The rejection of claims 1-12 under 35 U.S.C.112 1st paragraph (written description) has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1-12 under 35 U.S.C.112 2nd paragraph has been withdrawn has been withdrawn in light of Applicant's amendment of the claims.

Claims 1-12 and newly added claim 17 stand rejected under 35 U.S.C.112 1st paragraph (scope of enablement) for reasons set forth of the record mailed on 3/25/03 and further discussed below.

Claims 1-12 and newly added claim 17 stand rejected under 35 U.S.C. 103 (a) is maintained for reasons set forth of the record mailed on 3/25/03 and further discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the lowering of serum cholesterol or triglyceride levels in an individual comprising the steps of: preparing a nucleic acid construct comprising a DNA sequence encoding a fusion protein comprise a) a truncated form of a low

density lipoprotein but does not include the domain of the native protein associated with membrane binding or the domain associated with O-linked sugars, and b) a signal peptide which retains the fusion protein in ER, operatively linked to a promoter; administering the nucleic acid construct systemically to a mammal, wherein expression and production of said fusion protein results in the lowering of serum cholesterol in said mammal, and said nucleic acid construct, does not reasonably provide enablement for a method for lowering the serum cholesterol or triglyceride levels in an individual comprising the steps of: making such a genetic construct and delivering the genetic construct into an individual by any route. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to this rejection, Applicants argue that the current amended claims are limited to administering the fusion protein with ER localization signal. Applicants further assert that mouse is a widely accepted model for lipoprotein research. Applicants thus conclude the specification enables the claimed invention to its full scope.

These arguments have been fully considered and deemed partially persuasive. Thus, the enabled scope has been changed to a method for the lowering of serum cholesterol or triglyceride levels in an individual comprising the steps of: preparing a nucleic acid construct comprising a DNA sequence encoding a fusion protein comprise a) a truncated form of a low density lipoprotein but does not include the domain of the native protein associated with membrane binding or the domain associated with O-linked sugars, and b) a signal peptide which retains the fusion protein in ER, operatively linked to a promoter; administering the nucleic acid construct systemically to a mammal, wherein expression and production of said fusion protein results in

the lowering of serum cholesterol in said mammal, and said nucleic acid construct. However, Applicants are reminded that these arguments do not address the problem of route of delivery, which is important in the art of gene therapy (see page 6 of the previous office action). Therefore, the claims are not enabled to their full scope, and this rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Twisk et al., in view of Teasdale and Jackson and Attie et al. (5,521,071).

In response to this rejection, Applicants argue that neither Attie nor Twisk teaches what portion of the entire LDL receptor protein is responsible for the effect on apoB levels, thus it is not obvious that the truncated form of the LDL receptor would continue to interact with apoB in an individual. Applicants further argue that whether the level of localization of the LDL to ER by the signal peptide would be sufficient to locate the LDL receptor where it can interact with apoB is unknown, thus there is no reasonable expectation of success of the claimed method.

The above arguments have been fully considered, but they are not persuasive. The teachings of the cited references and the reasons for obviousness of the invention were discussed in detail in the previous office action. Contrary to Applicant's assertion, it is well known to one of ordinary skill of art that which portion of the LDL receptor interacts with apoB. Applicants in fact state in the arguments to the written description that "the prior art is generally aware of

extensive studies conducted on the LDL receptor and has exhaustively studied the fact that the LDL binding domain of the native protein is the first 242 amino acids of the protein." In addition, Attie teaches that ligand binding domain is generally associated with apoB 100 and apoE, and such ligand binding domain is well defined (see col 1 and 2, lines 42-68, and lines 1-11). As such, the soluble LDL receptor taught by Attie comprises such apoB binding domain, and it is obvious that it would interact with apoB in an individual.

Teasedale and Jackson not only teach ER retaining signal peptides, but also their mechanism of action. They teach "Each organelle of the secretory pathway is required to selectively allow transit of newly synthesized secretory and plasma membrane proteins and also to maintain a unique set of Resident proteins that defines its structural and functional properties In the case of the endoplasmic reticulum (ER), residency is achieved in two ways: (a) prevention of residents from entering newly forming transport vesicles and (b) retrieval of those residents that escape. The latter mechanism is directed by discrete retrieval motifs: Soluble proteins have a H/KDEL sequence at their carboxy-terminus; membrane proteins have a dibasic motif. either di-lysine or di-arginine, located close to the terminus of their cytoplasmic domain. Recently it was found that di-lysine motifs bind the complex of cytosolic coat proteins, COP 1, and that this interaction functions in the retrieval of proteins from the Golgi to the ER." (see abstract) In view of such teaching, there is reasonable expectation of success for the peptide attached to signal peptide such as KDEL to be localized in the ER. In view of the teaching by Twisk that rapid and slow presecretory apoB degradation may occur in the ER or in a post-ER compartment, one of ordinary skill of art would have reasonable expectation of success to make a fusion vector encoding a fusion protein of truncated LDL and KDEL, and have reasonable expectation of

success that said protein would locate in ER because of the KDEL signal and promotes the presecretory apoB degradation. Applicants are reminded that whether the invention has been done before is not evidence for the claimed invention to be non-obvious. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Therefore, for same reasons discussed in the previous office action, the claimed invention is *prima facie* obvious to one of ordinary skill of art at the time the invention was made. Thus, this rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER